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Review

Role of Mesolimbic Brain-Derived Neurotrophic Factor in Depression

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ABSTRACT

Brain-derived neurotrophic factor (BDNF) is widely accepted as being critical for neural and synaptic plasticity throughout the nervous system. Recent work has shown that BDNF in the mesolimbic dopamine (DA) circuit, originating in ventral tegmental area DA neurons that project to the nucleus accumbens, is crucial in the development of depressive-like behaviors following exposure to chronic social defeat stress in mice. Whereas BDNF modulates DA signaling in encoding responses to acute defeat stress, BDNF signaling alone appears to be responsible for the behavioral effects after chronic social defeat stress. Very different patterns are seen with another widely used chronic stress paradigm in mice, chronic mild stress (also known as chronic variable or unpredictable stress), where DA signaling, but not BDNF signaling, is primarily responsible for the behavioral effects observed. This review discusses the molecular, cellular, and circuit basis of this dramatic discrepancy, which appears to involve the nature of the stress, its severity and duration, and its effects on distinct cell types within the ventral tegmental area–to–nucleus accumbens mesolimbic circuit.

Keywords: Animal models, BDNF, Chronic mild stress, Depression, Dopamine, Electrophysiology, Individual differences, Mesolimbic dopamine circuit, Nucleus accumbens, Social defeat stress, Ventral tegmental area

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Brain-derived neurotrophic factor (BDNF) is the most extensively studied neurotrophin and is highly regulated in a neuronal activity–dependent manner (1). BDNF and its receptor, tyrosine receptor kinase B (TrkB), are expressed in the mesolimbic dopamine (DA) circuit, which projects from midbrain DA neurons in the ventral tegmental area (VTA) to the nucleus accumbens (NAc) in the basal forebrain (2,3). This mesolimbic BDNF-TrkB signaling pathway was first implicated in the actions of drugs of abuse more than 2 decades ago (4–6) and has more recently been associated with a range of motivation-related and natural reward-related behaviors, including consumption of food and social interaction (Figure 1A) (7,8). The mesolimbic DA circuit is activated by several forms of physical and social stress (8–10) as well as by natural and drug rewards (8,11–17). Increasing evidence suggests that interactions between BDNF-TrkB and DA signaling in the mesolimbic circuit play a critical role in stress-related and reward-related behaviors (15,16,18–20). There is also growing evidence for distinct subsets of VTA DA neurons, based in part on different inputs and outputs, which respond very differently to aversive versus appetitive stimuli and mediate very different responses to those perturbations (21–23).

Mesolimbic BDNF-TrkB signaling has been implicated as well in the pathophysiology of major depressive disorder (MDD) (24–28), for which antecedent stress is the strongest known risk factor (29,30). As loss of pleasure and motivation are core symptoms of depression in humans (31,32), it is not surprising that dysregulation of the mesolimbic DA system is associated with depression-related behaviors (28,31,33). Indeed, manipulation of BDNF-TrkB signaling in the mesolimbic DA system exerts robust effects on stress responses in animal models for depression, with activation of the pathway promoting depression-related behavioral abnormalities (8,10,11,34–36). Clinical evidence confirms these findings. Increased levels of BDNF protein in NAc are reported in patients with MDD at autopsy, including individuals who were depressed at the time of death despite taking antidepressants, suggesting elevated BDNF signaling as a sign of treatment-resistant MDD (11). Electroconvulsive therapy, one of the most effective treatments for depression, induces an antidepressant-like effect by reducing VTA BDNF expression (37). This prodepressant role for BDNF signaling in the mesolimbic circuit is opposite to the well-described antidepressant-like role in other brain regions, in particular, hippocampus [see (27,30,38,39)]. There is a high comorbidity of depression and drug addiction, and indeed studies support the involvement of BDNF in the VTA-to-NAc circuit in contributing to such interactions (40–48).

In this review, we highlight the actions of BDNF-TrkB signaling in the VTA-to-NAc DA system as a key mediator of depressive-like behaviors in the context of chronic stress. Furthermore, we discuss that exposure to different types of stress, through divergent interactions between BDNF and corticotropin-releasing factor (CRF) signaling, may differentially

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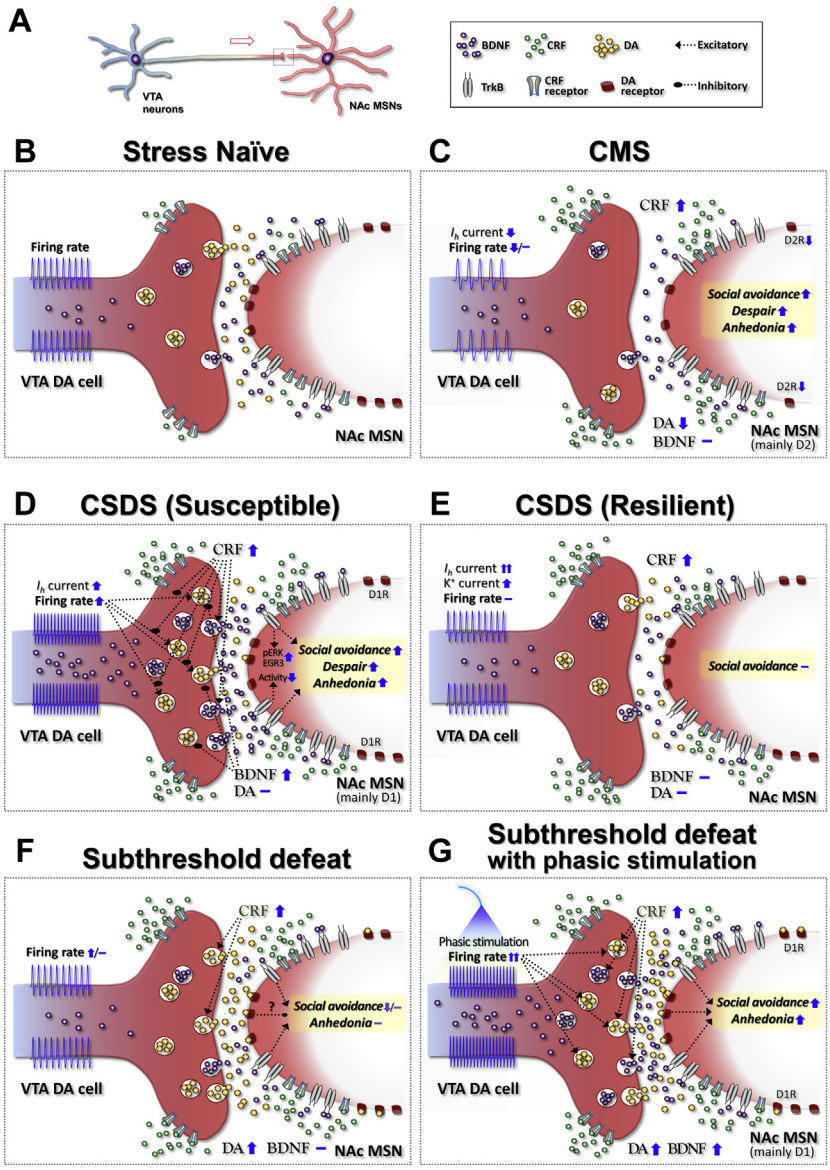

Figure 1. Role of brain-derived neurotrophic factor (BDNF) and its interactions with dopamine (DA) and corticotropin-releasing factor (CRF) in controlling the mesolimbic circuit after chronic stress. **(A)** The mesolimbic DA circuit, which is composed of DA neurons in the ventral tegmental area (VTA) and their forebrain projection regions, in particular, medium spiny neurons (MSNs) in nucleus accumbens (NAc), has been associated with depressive-like behavioral phenotypes, including social avoidance and anhedonia in animal models for depression. **(B, C)** Chronic mild stress (CMS) decreases hyperpolarization-activated cyclic nucleotide-gated channel-mediated currents (I_h) and firing rate of VTA-to-NAc DA neurons. Some clinical and preclinical studies show antidepressant-like effect of pramipexole, a D_2 receptor (D_2R) agonist, and relevance of mesolimbic D_2R signaling in CMS models, suggesting a functional role of D_2-MSNs in depressive symptoms (148–151). However, there are reports of selective effects of CMS on VTA–to–prefrontal cortex DA neurons (see text). **(D)** In contrast to CMS, animals susceptible to chronic social defeat stress (CSDS) display increased I_h and firing rate of VTA-to-NAc DA neurons and enhanced levels of NAc BDNF. Nonetheless, evoked DA release in NAc is not altered in susceptible animals, which may be due to homeostatic effects of CRF and BDNF in the mesolimbic circuitry. CRF, which elevates evoked DA release in NAc of stress-naïve animals, attenuates DA signaling in NAc in response to excessive and uncontrollable stress. This switch in CRF action may be mediated by changes in glucocorticoid signaling associated with chronic stress (not shown). Studies show that BDNF, but not DA, signaling in the mesolimbic system mediates CSDS-induced depressive behaviors. CSDS-induced BDNF signaling in NAc could contribute to behavioral susceptibility through extracellular signal-regulated kinase phosphorylation (pERK), early growth response 3 (EGR3) induction, and its consequential reduction in D_1-MSN activity. **(E)** Compared with susceptible animals, highly upregulated I_h, but with normal neuronal activity owing to a homeostatic induction of potassium (K^+) currents, are observed in VTA-to-NAc DA neurons of resilient mice. **(F, G)** In the subthreshold defeat stress paradigm, phasic activation of VTA DA neurons in general, or VTA-to-NAc DA neurons selectively, induces depressive-like behaviors, which is mediated through both BDNF and D_1R signaling. In contrast to CSDS, acute and weak stress manipulations, such as subthreshold defeat stress, elevate DA release via CRF in NAc (see text for details). In addition, CRF is required for NAc BDNF induction and consequent depressive behaviors by phasic activation of VTA-to-NAc neurons in subthreshold defeat stress. TrkB, tyrosine receptor kinase B.

regulate depressive-like behaviors based on cell type–specific actions within the mesolimbic circuitry.

MODELING FOR DEPRESSION IN RODENTS

MDD is a leading cause of severe social and economic burden that affects more than 300 million people worldwide (49). MDD is approximately 35% heritable, but this heritability is likely mediated by many hundreds of genes (50), each of which contributes a minute fraction to the overall risk. In the absence of a causative genetic factor of strong effect and high penetrance, the field has relied on several types of chronic stress paradigms in rodents based on epidemiological data, which show that early-life trauma and stressful life events are robustly correlated with high risk for depression, signifying aberrations in stress-coping capacity in patients with depression (51–57). A related approach is to expose rodents chronically to corticosterone to mimic one well-characterized concomitant of a chronically stressed state in some individuals (58).

Depression is highly heterogeneous, which makes it impossible for any single animal model to capture the entire human condition. Rather, the goal is to induce subsets of depression-like behaviors in animals (59). Some of the most prominent symptoms of depression (e.g., guilt, suicidality, and sad mood) are not accessible in animals. However, other symptoms of depression, schizophrenia, and autism spectrum

disorder (e.g., anhedonia; social withdrawal; and alterations in sleep, appetite, and circadian rhythms) are readily measurable in laboratory animals (60,61). Furthermore, these symptoms induced in rodents after chronic stress can often be ameliorated by administration of medications that are antidepressant in humans, with other classes of medication (e.g., anxiolytic drugs) being ineffective (62,63).

Traditionally, 3 criteria are used to judge the validity of an animal model (61). Construct or etiological validity refers to the model recapitulating the causes or mechanisms of a human condition. Face validity means that the model produces symptoms in animals that resemble symptoms of the human illness. Predictive validity indicates that the model reliably and accurately detects treatments that are clinically useful (64,65). It is important to note that the validation provided for a given model is fit for purpose because animal models are used for a variety of objectives, where, for example, construct or face validity may have a higher priority for researching potential etiology, whereas predictive validity is essential for medication testing (66). Difficulties in validating animal models for depression have been highlighted (61,67). Despite the healthy skepticism with which animal models of any psychiatric syndrome should be viewed, recent transcriptomic data have confirmed the ability of chronic stress models in rodents to recapitulate large subsets of gene expression abnormalities seen in human MDD (68), thus establishing that it is possible to induce significant portions of the molecular pathology of human depression in rodent models.

Historically, most studies used acute stress assays, such as the forced swim and tail suspension tests (69–71), to study depression-related phenomena, particularly to screen for potential antidepressant compounds, owing to their ease, automation, and rapid phenotyping abilities (60). However, these tests cannot be viewed as models for depression: they use acute stresses (which generally do not cause depression), and monoamine-based antidepressants work in these assays after single doses, even though their clinical efficacy requires weeks or months of treatment (60,72). For these reasons, the field has turned increasingly to a variety of chronic stress models, which show better construct and face validity as well as better predictive validity in that they respond only to repeated administration of monoamine-based antidepressants. Moreover, as stated earlier, studies of human postmortem samples have shown that chronic stress paradigms induce molecular, cellular, and circuit abnormalities seen in human depression (11,13,68,73,74). Other models for the study of depression have focused on periods of early life stress (75,76), which are not covered here because there has been less exploration of the influence of BDNF-TrkB signaling in these paradigms.

ROLE OF VTA DA NEURON ACTIVITY IN CHRONIC STRESS MODELS: CHRONIC MILD STRESS VERSUS CHRONIC SOCIAL DEFEAT STRESS

Chronic mild stress (CMS)—also referred to as chronic variable or unpredictable stress—is one of the most widely used chronic stress–based animal models for depression (77). In the CMS model, animals are subjected to varied and intermittent physical stressors, such as forced swim, cage tilt, cage crowding, and water and food deprivation over a period of time that ranges from 1 to 12 weeks (60,78,79). Animals exposed to CMS display increased immobility in the forced swim and tail suspension tests and a decrease in social interaction and sucrose preference, used as rough measures of anhedonia (38,80–82). More precise determinations of anhedonia would involve more time-consuming operant behaviors, which have rarely been used in the field but represent an important goal for future studies. Mice exposed to CMS exhibit decreased activity of VTA DA neurons (80,82), an effect observed in brain slices ex vivo and in awake mice in vivo. Acute, optogenetic phasic (30 Hz) stimulation of VTA DA neurons reverses the CMS-induced abnormalities in sucrose preference and tail suspension tests (Figure 1B, C) (38,80,82). In contrast, optogenetic inhibition of VTA DA neurons in stress-naïve mice reduces sucrose preference and increases immobility (80).

A recent study with brain slices ex vivo has shown that the reduced firing activity of VTA DA neurons seen after CMS is specific for VTA-to-prefrontal cortex (PFC) DA neurons, with no effect observed for VTA-to-NAc DA neurons (38). A similar lack of effect of CMS was found for the lateral VTA (83), where DA neurons project predominantly to NAc (84). In contrast, other studies found significant reductions in firing rate and burst firing in lateral VTA DA neurons after CMS (80,82). This discrepancy may be due to differences in the CMS paradigms used: the former studies applied 3 to 4 stressors per week over 4 weeks in rats (83) and 5 to 7 stressors per week over 5 weeks in mice (38), whereas the latter studies applied 14 stressors per week over 5 weeks in mice (82) and 14 stressors per week over 8 to 12 weeks in mice (80).

The reported differences in neural activity between VTA-to-NAc and VTA–to–medial PFC circuits following CMS may be partly due to differences in expression of ion channels between circuits. Recent studies demonstrated that there are large hyperpolarization-activated cyclic nucleotide-gated channel-mediated currents (I_h) in VTA-to-NAc DA neurons, but small or no I_h in VTA–to–medial PFC DA neurons (84,85). Pharmacological manipulations that increase I_h in VTA DA neurons increase firing frequency (85–88). CMS reduces I_h in VTA-to-NAc DA neurons (82), with a consequential reduction of DA release in NAc (89). Likewise, short hairpin RNA–mediated knockdown of hyperpolarization-activated cyclic nucleotide-gated channel 2 in VTA mimics CMS-induced depressive-like behavior in stress-naïve mice, whereas overexpression of hyperpolarization-activated cyclic nucleotide-gated channel 2 in VTA prevents the CMS-induced behavioral deficits (82). These findings emphasize that reduction in DA signaling in the VTA-to-NAc DA pathway contributes to depressive-like behaviors induced by CMS (Figure 1C), although as noted in the previous paragraph there are studies that suggest a predominant effect of CMS on VTA-to-PFC DA neurons. The ion channel mechanisms that underlie stress-induced regulation of VTA-to-PFC DA neurons remain unknown.

In contrast, very different effects are seen after chronic social defeat stress (CSDS), another well-established mouse model for depression (8,11). CSDS for 10 days causes social avoidance in a subset of mice, which are designated as susceptible to CSDS, with the remainder designated as resilient. The susceptible mice also exhibit reduced sucrose preference and disrupted circadian, sleep, and feeding behavior

compared with resilient and stress-naïve control mice (8,11,60,90,91). Strikingly, susceptible mice exhibit increased firing activity and burst firing in VTA DA neurons in brain slices ex vivo and in anesthetized mice in vivo, respectively (Figure 1D) (9–11,88,92–94). Moreover, this effect is specific for VTA-to-NAc DA neurons, with the opposite effect—a reduction in firing activity—observed for VTA-to-PFC DA neurons (10). Optogenetic inhibition of VTA DA neurons in general, or VTA-to-NAc DA neurons specifically, in susceptible mice induced a rapid antidepressant-like response: the manipulation increased social interaction and sucrose preference behaviors (10). Conversely, in a 1-day subthreshold SDS (sub-SDS) procedure that does not induce behavioral abnormalities, phasic activation of either VTA DA neurons in general, or VTA-to-NAc DA neurons specifically, during the social interaction test induced depressive-like behavior, effects not seen in stress-naïve control mice (10,34). These lines of evidence that VTA-to-NAc and VTA-to-PFC pathways have distinct functional properties and differentially regulate behavior suggest that aversive stimuli differentially affect these microcircuits and that the final behavioral output results from the balance between these circuits.

In contrast to CMS, CSDS increases I_h in VTA DA neurons of both susceptible and resilient mice compared with non-stressed control mice (9,85). The enhanced I_h increases VTA DA neuron activity and DA release in NAc (Figure 1D) (85–87,95). It is of particular interest that resilient mice display a greater magnitude of induction of I_h in VTA DA neurons compared with susceptible mice and that this greater induction of I_h triggers stable normal firing of VTA DA neurons in resilient mice. This occurs via the homeostatic induction of several types of potassium (K^+) channels in the resilient VTA, which normalizes VTA DA neuron firing and promotes resilience to defeat stress (Figure 1E) (11,85). Overexpression of the inwardly rectifying K^+ channel Kir2.1 in VTA of susceptible mice decreases the firing rate of VTA DA neurons and blocks social avoidance behaviors (11), similar to intra-VTA infusion of an inhibitor of I_h (9). Studies in primary neuronal cultures have reported that excessive hyperactivity can induce homeostatic upregulation of K^+ channel–mediated current (96). Our observation that elevated K^+ current attenuates the I_h-induced increase in DA neural activity in resilient mice suggests that homeostatic plastic processes occurring in the mesolimbic region stabilize neural dynamics (85).

Recent evidence further highlights the role of ion channels in VTA DA cells in mediating resilience to social stressors. Overexpression of KCNQ3 (Kv7.3), a slow voltage-activated K^+ channel that is induced in VTA of resilient mice (11), specifically in VTA DA neurons of susceptible mice, reversed both the increased firing of VTA DA neurons and the depressive-like phenotype (97). Thus, targeting KCNQ channels offers a novel approach for depression treatment, as intra-VTA infusion or systemic administration of KCNQ channel openers, including the U.S. Food and Drug Administration–approved drug retigabine (also called ezogabine, originally approved as an antiepileptic drug) (98), normalized depression-like behaviors in susceptible mice (97). A recent open-label clinical trial with 18 medication-free patients with MDD found that retigabine had significant antidepressant efficacy, along with normalizing depression-related functional connectivity abnormalities in the brain's reward circuitry (99), a finding now being followed up with a placebo-controlled study. These clinical data should be viewed with caution, as retigabine has several side effects (98); however, the observations demonstrate the ability to apply insight derived from rodent stress models to novel approaches for the treatment for depression (74,99).

The differences observed in VTA DA neuron activity and in I_h in these cells after CMS versus CSDS might be explained by the type and intensity of the stressor as well as by the duration of stress exposure (79,100,101). Strong stress increases VTA DA neural activity (102), whereas milder stress decreases it (94,103). These findings likely correlate with observations that CMS, which typically consists of exposing mice to a variety of weak but uncontrollable stressors, decreases VTA DA neural activity, whereas CSDS, which consists of more severe and socially relevant stress, increases such activity. However, we observed that evoked DA release in NAc is not significantly altered by CSDS, which may reflect a ceiling effect of CSDS increased phasic firing of VTA DA neurons in vivo (35). This discrepancy between DA release and DA neural activity following CSDS may also be related to CRF, a neuropeptide released in response to stress (104) that may play a prominent role in regulating DA neural activity or DA release. CRF positively mediates rewarding behavior by enhancing I_h in VTA DA neurons, which leads to elevated evoked DA release in NAc of stress-naïve animals (95). In contrast, exposure to severe stress completely ablated the CRF effects on DA release and subsequent appetitive behaviors (105). This switch in CRF action on DA release is mediated in part by glucocorticoid signaling associated with severe and chronic stress (105).

ROLE OF BDNF AND CRF IN CSDS: ACUTE VERSUS CHRONIC ACTIONS

Both CMS and CSDS, as described above, show causal evidence that acute manipulations of VTA DA neurons can alter depressive-like behaviors in a range of behavioral assays (106). However, there are some intriguing reports that DA-deficient mice (generated through loss of DA-synthetic enzymes) can still learn and express preferences for sucrose (107) and that pharmacological depletion or antagonism of mesolimbic DA signaling does not alter sucrose preference in stress-naïve animals (108). These data suggest that DA per se is not always the critical mesolimbic substrate in some types of stress-based depression models.

As noted earlier, CSDS increases BDNF protein levels and BDNF-TrkB signaling in NAc, effects that are dependent on the *Bdnf* gene in VTA DA neurons (8,11). Knockout of *Bdnf* in VTA blocks behavioral susceptibility to CSDS and exerts antidepressant-like effects (Figure 1D) (8,11,37). Blockade of BDNF-TrkB signaling in NAc also has an antidepressant-like effect (11,35,36), whereas increasing BDNF levels in NAc produces prodepressant effects (11). These actions of mesolimbic BDNF in the CSDS model are in striking contrast to the lack of influence of BDNF in the CMS model (38,109). For example, CMS does not alter protein levels of BDNF in either NAc or VTA (109). BDNF infusion into NAc shell has no impact on CMS-induced depressive-like behaviors (38).

Insight into the relative contributions of DA and BDNF to stress responses comes from a study, which demonstrated that

BDNF-TrkB, but not DA, signaling in NAc is essential for CSDS-induced depressive-like abnormalities (35). Chronic optogenetic phasic stimulation of VTA-to-NAc circuit during CSDS exacerbated defeat-induced behavioral symptoms, and these aggravated symptoms were reversed by blockade of BDNF-TrkB signaling in NAc. By contrast, optogenetic activation of VTA-to-NAc DA neurons during CSDS, or CSDS itself, did not alter evoked NAc DA release (35). Additionally, intra-NAc infusion of DA receptor antagonists had no effect on CSDS-induced depressive-like symptoms (35). This inability of DA signaling to affect CSDS-induced depressive-like behaviors is very different from sub-SDS, where intra-NAc administration of DA receptor antagonists blocked the ability of acute optogenetic stimulation of VTA-to-NAc neurons to induce depressive-like behaviors following sub-SDS (Figure 1D, G) (35). This difference in the role of mesolimbic DA signaling between sub-SDS and CSDS may be due to mesolimbic BDNF normalizing stress-induced extracellular DA release in NAc, where CSDS-induced BDNF signaling in the VTA-to-NAc circuit may attenuate DA release that can be facilitated by heightened mesolimbic DA activity, a mechanism supported by studies in $BDNF^{+/-}$ mice (110–112).

In contrast, the significant effect of DA signaling on depressive-like behaviors in sub-SDS could be associated with lack of involvement of CRF, as regulation of the mesolimbic system by CRF becomes prominent only after severe, chronic stress (35,105). One day of sub-SDS compared with CSDS may not be long enough for CRF action to switch from appetitive to aversive. In other words, in contrast to CSDS, 1-day sub-SDS increases DA activity in the context of normal CRF action, mediating appetitive behaviors (92,105,113), which may explain the previous observation that sub-SDS sometimes increases social interaction (Figure 1F) (11,114). Observations that phasic stimulation of VTA-to-NAc DA neurons, following sub-SDS, requires NAc BDNF signaling in order to induce depression-like behavior, whereas intra-NAc infusion of a CRF receptor antagonist reverses both social avoidance and BDNF release, suggest an intimate interaction between these systems in encoding for the actions of acute stressors (Figure 1G) (34).

DOWNSTREAM TARGETS OF BDNF ACTIVATION—D_1 VERSUS D_2 MEDIUM SPINY NEURONS

Principal NAc neurons are categorized as D_1-type or D_2-type medium spiny neurons (MSNs) based on the predominant DA receptor that they express. In general, D_1-MSNs send projections to VTA and to a lesser extent to ventral pallidum, whereas D_2-MSNs send projections to ventral pallidum (115,116). These two neural populations work in concert to control behavior, with an imbalance promoting dysfunctional motivational states (117–121). In general, activation of D_1-MSNs promotes rewarding behavior, whereas activation of D_2-MSNs exerts the opposite effect (118,121–125).

Stress exposure has also been shown to differentially affect these neuronal subtypes. D_1-MSNs were shown to be the site of action of BDNF in NAc following CSDS exposure. Levels of phosphorylated (active) extracellular signal-regulated kinase, a downstream target of TrkB receptor signaling, are increased solely in NAc D_1-MSNs of susceptible, but not resilient, mice (35,97). These observations suggest that BDNF signaling in D_1-MSNs contributes to the susceptible phenotype after CSDS (Figure 1D). Interestingly, enhanced extracellular signal-regulated kinase phosphorylation has been associated with reduced neuronal activity of D_1-MSNs (121), and reducing neuronal activity of D_1-MSNs renders resilient mice more susceptible (125). Moreover, excitatory synaptic input to D_1-MSNs is reduced in susceptible mice after CSDS (125) and in mice subjected to repeated restraint stress (126), both of which induce anhedonia-like behaviors. Together, these results support a scheme wherein increased BDNF signaling in NAc contributes to CSDS-induced behavioral susceptibility by inhibiting the activity of D_1-MSNs. In vivo imaging studies report decreased activity of D_1-MSNs of susceptible mice (127). In contrast, enhanced activity of D_1-MSNs encodes pro-reward and reinforcement behaviors (121,125,126,127–130). D_2-MSNs exhibit increased excitatory synaptic input in susceptible mice after CSDS, which suggests possible differences in the effects of phasic VTA DA input to D_1-MSNs versus D_2-MSNs in NAc. In other words, it is possible that elevated BDNF release from VTA DA nerve terminals in NAc in response to CSDS has differential effects on D_1-MSNs and D_2-MSNs resulting in the expression of depression-like behaviors.

The transcription factor early growth response 3 (EGR3) is another promising downstream target of mesolimbic BDNF activation (131). Following exposure to CSDS, EGR3 is upregulated in NAc D_1-MSNs, but not D_2-MSNs, of stress-susceptible mice (127). Furthermore, elevated EGR3 appears to be responsible for the observed decreased excitatory input and increased dendritic atrophy in D_1-MSNs of stress-susceptible mice (127). EGR3 regulates the expression of several proteins involved in synaptic plasticity, and chromatin immunoprecipitation coupled with short-tag sequencing analysis found that stress exposure altered EGR3 binding to promoter regions of genes involved in dendritic morphology, such as *Actn1*, *RhoA*, and *Shank2* (127,132,133). In light of earlier work that stress-susceptible mice exhibit elevated phasic activity of VTA DA neurons (10,11) and concomitant enhanced levels of BDNF release from VTA DA terminals in NAc (11,34), it is possible that the elevated BDNF induces EGR3 in D_1-MSNs leading to decreased excitatory input and increased dendritic atrophy (127) and subsequent expression of depression-like behavior (Figure 1D).

Exposure to CSDS differentially induces expression of another transcription factor, ΔFosB, a Fos family protein that accumulates in NAc in response to repeated stimuli associated with reward, motivation, or stress (134). Mice susceptible to CSDS exhibit ΔFosB induction selectively in D_2-MSNs, whereas mice resilient to CSDS show ΔFosB induction solely in D_1-MSNs (135). Chronic exposure to drugs of abuse also induces ΔFosB expression in NAc, with effects predominating in D_1-MSNs, although opiate drugs of abuse and natural rewards induce the protein in both cell types (135,136). A recent study investigated whether the observed comorbidity between addiction and depression may be related to overlapping signaling between BDNF and ΔFosB within the mesolimbic circuit. This study followed up on previous observations that intra-VTA BDNF overexpression enhanced SDS-induced cross-sensitization to psychostimulants together with induced ΔFosB expression in NAc

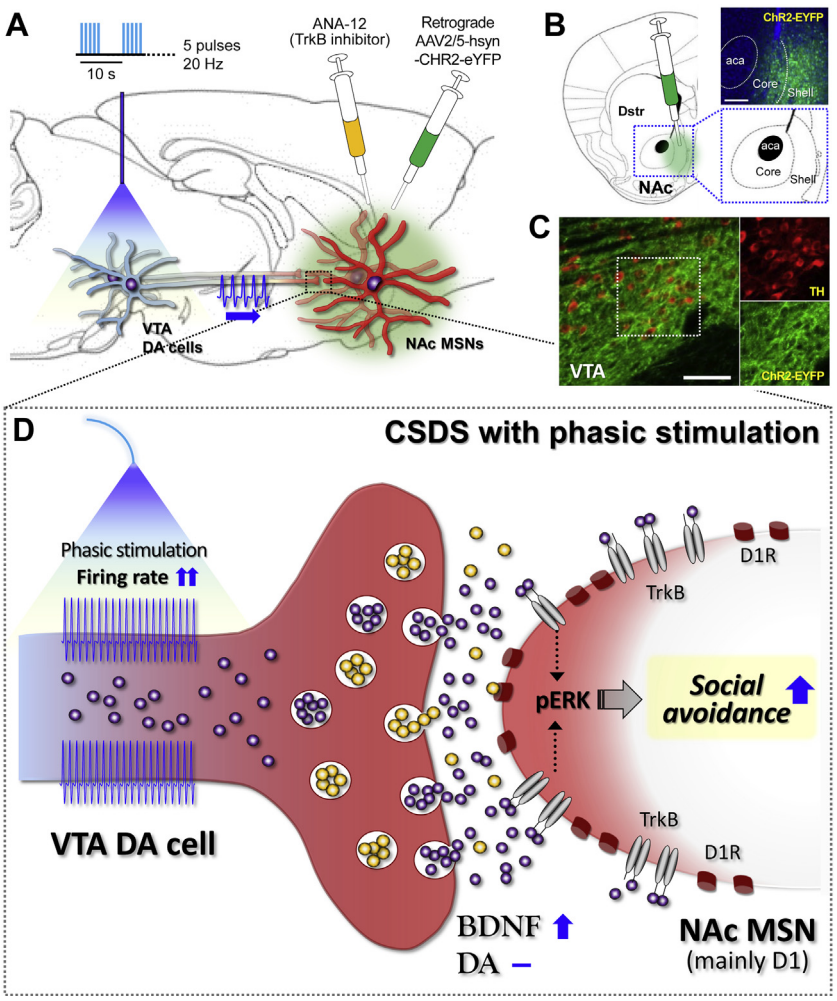

Figure 2. Working model of behavioral abnormalities (e.g., social avoidance) that are exacerbated by repeated phasic optogenetic stimulation of ventral tegmental area (VTA)–to–nucleus accumbens (NAc) dopamine (DA) pathway during chronic social defeat stress (CSDS). **(A)** Illustration of retrograde adeno-associated virus vector AAV2.5-hsyn-ChR2-eYFP infused into NAc, intra-NAc ANA-12 infusions, and optic fiber implantation into VTA. Blockade of D_1 receptor (D_1R) or D_2 receptor signaling in NAc does not affect social avoidance induced by CSDS, but inhibition of brain-derived neurotrophic factor (BDNF)–tyrosine receptor kinase B (TrkB) signaling in NAc using ANA-12 reverses this behavioral abnormality (35). Impaired social interaction after CSDS was exacerbated by repeated phasic activation of VTA-to-NAc pathway. Inhibition of BDNF-TrkB signaling blocked this effect of optogenetic stimulation. **(B)** Schematic coronal sections showing injection site of AAV2.5-hsyn-ChR2-eYFP in NAc. Scale bar = 100 μm. **(C)** Representative confocal images showing localization of ChR2-EYFP (green) in tyrosine hydroxylase (TH)–positive cells (red) in VTA. Scale bar = 50 μm. **(D)** Illustration of CSDS-induced social avoidance behavior that is exacerbated by repeated phasic optogenetic stimulation of VTA-to-NAc DA pathway. NAc BDNF mediates social avoidance through activation of TrkB on D_1 medium spiny neurons (MSNs), as evidenced by exclusive induction of extracellular signal-regulated kinase phosphorylation (pERK) in D_1-MSNs of susceptible mice (35). aca, anterior part of anterior commissure; ChR2, channelrhodopsin-2; Dstr, dorsal striatum; eYFP, enhanced yellow fluorescent protein.

(137). The authors showed that although stress exposure increased cocaine intake, rats exposed to SDS together with increased expression of VTA-BDNF exhibited even greater cocaine intake and increased ΔFosB expression in NAc. BDNF-TrkB signaling in NAc activates the transcription factor cAMP-response element binding protein (138,139), as would be expected, as cAMP-response element binding protein activation is known to be downstream of TrkB activation. The observation that cAMP-response element binding protein induces ΔFosB transcription (140,141) and itself can promote depression-like behavior at the level of VTA-to-NAc circuit (28) suggests complex feedback loops that operate within NAc MSNs—in a cell type–specific manner—to control the influence of BDNF in this circuit and the generation of both depression-like and addiction-like behavioral abnormalities. It should be noted that in addition to distinct D_1-MSNs and D_2-MSNs, there is also a small subpopulation of cells that express both D_1 receptors and D_2 receptors in NAc, along with reports that functional D_1 receptor and D_2 receptor dimers contribute to regulation of these cells.

Stress hormones also play a role in regulating circuits connecting stress signaling to the mesolimbic system. Certain depression-like behaviors (e.g., social avoidance) after chronic stress require activation of glucocorticoid receptors (GRs) on NAc MSNs (142). Knockout of GRs from MSNs, but not VTA DA cells, alleviated CSDS-induced depression-like, but not anxiety-like, behaviors. Building on previous studies (9–11,34,85), Barik *et al.* (142) observed increased VTA DA neural activity in vivo following exposure to CSDS, which was lost upon GR knockout from MSNs. That GR knockout in MSNs alleviates the CSDS-induced increase in VTA DA activity suggests a feedback mechanism from NAc to VTA. Further work is needed to determine whether this normalization of VTA DA neuron activity is mediated by their direct innervation by MSNs or by indirect effects of MSNs on VTA inhibitory interneurons.

CONCLUSIONS AND FUTURE DIRECTIONS

Today's antidepressant treatments fully treat <50% of affected individuals (143–145). The highly heterogeneous nature of depression has prompted preclinical and clinical

researchers to use multiple stress paradigms and clinical measures to define diverse mechanisms that contribute to the etiology of depression toward the goal of more personalized treatments in the future (24). From the preclinical side, for example, work described here has distinguished between acute and chronic stress paradigms (35) and between stress-susceptible and stress-resilient animals subjected to stress (11,146). Types, intensity, duration, and incubation period of stress have been considered as contributing factors (79,100,147).

We speculate that the strength of stressors is a key determinant of the effects on VTA DA neuron activity. Severe stress increases VTA DA neural activity (102), whereas mild stress decreases it (94,103). These findings are consistent with observations that CMS decreases VTA DA neural activity, whereas CSDS increases it. Of note is our 2016 study showing that DA release is no longer relevant to the CSDS-induced increase in phasic firing of VTA DA neurons, as evoked DA release in NAc is not significantly altered by CSDS owing to compensating mechanisms (Figure 2). In addition, mesolimbic DA signaling was found not to mediate CSDS-induced behavioral abnormalities (35). The lack of DA release and of effects of functional DA signaling in NAc following CSDS may be related to CRF, as homeostatic regulation over the mesolimbic system by CRF is revealed only after severe, chronic stress (105). It may also be due to homeostatic effects of BDNF on the excitability of DA neurons or on extracellular DA release as observed in previous studies (15,110–112). Understanding these homeostatic functions of CRF and BDNF and their concomitant interaction in CSDS warrants further investigation.

Current evidence thus supports a scheme where mesolimbic BDNF, which is induced only in susceptible mice after CSDS, contributes importantly to the behavioral sequelae of CSDS, independently of DA signaling. However, this hypothesis raises further questions. What are the molecular and physiological mechanisms that elevate mesolimbic BDNF in response to CSDS? As discussed above, NAc CRF is one candidate to induce mesolimbic BDNF and downstream depressive-like behaviors (34). Alternatively, does NAc CRF act directly on NAc MSNs to induce behavioral susceptibility to CSDS? If so, are D_1-MSNs, where BDNF-TrkB signaling mediates the behavioral effects of CSDS, also important for CRF action? It would be interesting to investigate whether CRF-induced release of BDNF from VTA DA nerve terminals into NAc of stress-susceptible mice decreases expression of ΔFosB in D_1-MSNs or induces ΔFosB in D_2-MSNs to also contribute to the susceptible versus the resilient phenotype (134,135). Taken together, investigating the dynamics of mesolimbic BDNF signaling and its interactions with numerous other molecular and cellular mechanisms in this circuit has provided important insight into the biological mechanisms of susceptibility and resilience in response to diverse types of stress, work that is also being mined for developing more effective and better-targeted therapeutics for depressive disorders.

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